ORIGINAL RESEARCH

American Heart Association | American Stroke Association

Left Ventricular Hypertrophy Regression During Antihypertensive Treatment in an Outpatient Clinic (the Campania Salute Network)

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***Background*—**Regression of left ventricular (LV) hypertrophy (LVH) has been a goal in clinical trials. This study tests the external validity of results of clinical trials on LVH regression using a large registry from a tertiary care center, to identify phenotypes less likely to achieve regression of LVH.

***Methods and Results*—**Patients from the Campania Salute Network, free of prevalent cardiovascular disease, but with echocardiographic LVH (defined as LV mass index [LVMi] >47 g/m$^{2.7}$ in women and >50 g/m$^{2.7}$ in men) were included. During a median follow-up of 67 months, clear-cut regression of LVH was documented in 14% of patients (13±8% reduction of initial LVMi) or 23% when also considering those with a reduction of LVMi ≥5 g/m$^{2.7}$. Patients with persistent LVH were older with longer duration of hypertension, suboptimal blood pressure (BP) control, larger body mass index, LV mass, and carotid intima-media thickness and included more women and subjects with diabetes mellitus, isolated systolic hypertension, and metabolic syndrome (all $P<0.05$). Number and class of antihypertensive drugs during follow-up did not differ between groups. In multiple logistic regression analysis, older age, female sex, obesity, higher baseline LVMi and carotid intima-media thickness, and suboptimal BP control were significant covariates of persistent LVH (all $P\leq0.01$), independent of diabetes, duration of hypertension, isolated systolic hypertension, follow-up time and number and class of antihypertensive drugs.

***Conclusions*—**Early initiation of antihypertensive treatment, aggressive BP control, and attention to metabolic aspects are critical to avoid irreversible LVH. **(*J Am Heart Assoc*. 2017;6:e004152. DOI: 10.1161/JAHA.116.004152.)**

Key Words: antihypertensive therapy/central agents • echocardiography • left ventricular hypertrophy • left ventricular hypertrophy regression • regression

Left ventricular (LV) hypertrophy (LVH) is a risk predictor in hypertension,[1,2] and clinical trials have demonstrated that LVH regression during antihypertensive treatment reduces cardiovascular morbidity and mortality.[3–5] Thus, LVH regression is considered a therapeutic target and a reversible risk marker in hypertension.[6] Some studies indicate that different classes of antihypertensive medication might differ in their ability to promote LVH regression.[7,8] However, most interesting, a number of studies have demonstrated that LVH regression is not always achieved, even when blood pressure (BP) is optimally controlled, in particular, in women and obese subjects.[9–11] Recently, results from the Strong Heart Study, a population-based cohort, including hypertensive patients with multiple cardiovascular risk factors and comorbidities, demonstrated an average increase in LV mass (LVM) during follow-up, even in the subpopulation with optimal BP control.[11] These findings suggest that in the real world, there might be problems in achieving effective LVH regression, which are not explored in clinical trials that are conducted in selected hypertensive populations.[12]

Accordingly, we analyzed a large series of treated hypertensive outpatients with established LVH from a tertiary care center, to test the external validity of the results of clinical trials on LVH regression and identify the clinical phenotypes less likely to achieve LVH regression during antihypertensive treatment.

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Accompanying Tables S1 through S4 are available at http://jaha.ahajournals.org/content/6/3/e004152/DC1/embed/inline-supplementary-material-1.pdf

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Methods

Study Population

The Campania Salute Network (CSN) is an open registry collecting information from general practitioners and community hospitals networked with the Hypertension Center of the Federico II University Hospital (Naples, Italy).[13] Characteristics of the registry have been previously reported in detail.[14] Briefly, the database generation was approved by the Federico II University Hospital Ethic Committee and signed informed consent to use data for scientific purposes was obtained from all participants. At the time of the present analysis, 14 055 hypertensive patients aged ≥18 years were registered in the CSN. After excluding patients with prevalent cardiovascular disease (n=3531), less than 24 months of follow-up (n=4729), and patients without LVH at baseline (n=3622), the final study population consisted of 2173 hypertensive patients with ascertained LVH at the first echocardiogram performed at the time of the first visit, at the enrollment into the registry.

Clinical and Laboratory Examinations

Systolic (SBP) and diastolic BP (DBP) were measured in the sitting position by a calibrated aneroid sphygmomanometer after 5 minutes of resting. Consistent with the current guidelines,[6] BP was measured 3 times at 2-minute intervals and the average of the last 2 BP was taken as the office BP. Isolated systolic hypertension (ISH) was defined as baseline SBP ≥140 mm Hg and baseline DBP <90 mm Hg. BP was considered optimally controlled when office SBP was, on average, <140 mm Hg and DBP, on average, <90 mm Hg as the mean of measurements in the control visits during the follow-up.

Fasting lipid and glucose profile was measured by standard methods. Body mass index (BMI) was calculated as body weight divided by height in squared meters, and obesity was defined as BMI ≥30 kg/m^2. Metabolic syndrome (MetS) was defined according to the modified ATPIII criteria,[15] substituting waist circumference with BMI ≥30 kg/m^2, as previously done when waist circumference was not available.[16,17] Glomerular filtration rate (GFR) was estimated using the simplified Modification of Diet in Renal Disease formula.[18]

Antihypertensive Medication

Number and type of prescribed antihypertensive medication were recorded for all participants during initial and control visits. Classes of medications included anti-renin–angiotensin system medications (angiotensin-converting enzyme [ACE] inhibitors and/or angiotensin AT1 receptor blockers [ARB]), calcium (Ca)-channel blockers (CCBs), beta-blockers, and diuretics. All classes were considered according to their overall use during the individual follow-up, based on the frequency of prescription during the control visits (every 4 months–1 year interval). As previously reported,[19,20] all medications that were prescribed in more than 50% of the follow-up visits were considered in the analysis as part of the treatment in the individual patient.

Echocardiography

Echocardiograms were performed at the time of the initial visit in the Hypertension Center and at the follow-up visits using commercially available machines by a standardized protocol. Patients underwent a number of echocardiograms during follow-up (at least once a year). Quality-controlled validation was performed for echocardiographic exams performed at the enrollment in the registry (baseline), at the last available echocardiogram before a censored event, or at the time of the last available visit before the present database generation. As previously reported,[21,22] echocardiograms were recorded on videotapes, stored digitally, and read offline by 1 expert reader under the supervision of a senior faculty member on dedicated workstations (MediMatic, Genova, Italy). Measurements were made according to the joint American Society of Echocardiography/European Association of Echocardiography recommendations.[23] LVM was calculated from a necropsy-validated formula[24] and indexed for height in meters to the power of 2.7 (LV mass index; LVMi).[25] Relative wall thickness was computed as posterior wall thickness/LV end-diastolic radius, and concentric LV geometry was defined as relative wall thickness ≥0.43.[26] Regression of LVH was adjudicated when LVMi was <50 g/m$^{2.7}$ in men and <47 g/m$^{2.7}$ in women[27] at the time of the last available visit of the follow-up. Alternative analyses were run pooling patients with follow-up LVMi reduction of at least 5 g/m$^{2.7}$ with those normalizing LVMi.

Arterial stiffness was estimated as the ratio between brachial pulse pressure and stroke index, as previously reported.[28]

Carotid Ultrasound

Carotid ultrasound was performed as previously reported.[29] Briefly, patients were accommodated in the supine position with the neck extended in mild rotation. The scanning protocol was performed with an ultrasound device (SONOS 2500/5500; HP, Philips, Best, The Netherlands) equipped with a 7.5-MHz high-resolution transducer with an axial resolution of 0.1 mm. Examinations were recorded on S-VHS videotapes and analyzed offline using an image-processing dedicated workstation (MediMatic). The maximal arterial intima-media thickness (IMT) was estimated in up to 12

arterial walls, including the right and the left, near and far distal common carotid, bifurcation, and proximal internal carotid artery as previously described in detail.[29]

Statistical Analysis

Data were analyzed using SPSS software (version 22.0; SPSS, Inc., Chicago, IL) and continuous variables are reported as mean±1 SD or by median and interquartile range (IQR), for variables deviating from normal distribution, whereas categorical variables were reported as percentages. Descriptive statistics are presented in patients with or without LVH regression, using *t* test and chi-squared statistics, as appropriate. For skewed variables, the nonparametric Mann–Whitney *U* test was used.

Univariate logistic regression was used to identify significant association with lack of LVH regression. Forward step-wise multivariable logistic regression analysis, including covariates identified in univariate logistic analysis, was used to identify independent factors associated with lack of regression of LVH. In a second model, we also forced in the number of antihypertensive drugs and single classes of medications. The same procedure was adopted for the other criterion (including reduction of at least 5 $g/m^{2.7}$ or normalization of LVMi).

Cox regression analysis was used to assess whether lack of LVH regression was associated with higher risk of incident cardiovascular events (fatal and nonfatal myocardial infarction, stroke and heart failure, angina, transient ischemic attack, myocardial or carotid revascularization, and atrial fibrillation). The same analysis was also performed considering normalization or ≥5 $g/m^{2.7}$ reduction of initial LVMi. Assessment of LVMi was done at the time of either the last available echocardiogram or the echocardiogram immediately preceding the occurrence of the first cardiovascular event.

Results

Prevalence and Prognostic Impact of LVH Regression

The study population consisted of 2173 hypertensive patients with mean age 57±10 years and 48% were women. During a median follow-up of 7.0 (IQR, 5.0–12.0) years, LVH regression was achieved in 295 patients (14%), though optimal BP was achieved in 1898 (87%). Considering also a reduction of initial LVMi ≤5 $g/m^{2.7}$, the proportion of patients with significant reduction of LVMi increased to 489 (ie, 23%). In the total study population, follow-up reduction in SBP was −9±17 mm Hg, in DBP was −6±10 mm Hg, and in LVMi was −9.1±10.8 $g/m^{2.7}$. Patients with LVH regression had a mean reduction of 13±8% in LVMi compared to a slight increase of 2±10% in LVMi in the group of participants without LVH regression ($P<0.001$).

During follow-up, a total of 185 cardiovascular events occurred. In Cox regression analysis, adjusting for age and sex, lack of LVH regression was associated with higher hazard rate of cardiovascular events (hazard ratio [HR], 1.71 [95% CI 1.05–2.78]; $P=0.03$). Similarly, in the alternative analysis, lack of either reduction or normalization of LVMi was associated with increased hazard of cardiovascular events (HR, 1.56 [95% CI 1.06–2.28]; $P=0.02$).

Clinical Phenotypes of Patients With Lack of LVH Regression

Patients who did not experience LVH regression were older, had longer duration of hypertension, higher baseline SBP and BMI, and included more women and subjects with diabetes mellitus, obesity, ISH, and MetS (all $P\leq0.001$; Table 1). Smoking habit was less frequent and follow-up time shorter among patients who did not achieve regression of LVH ($P<0.04$; Table 1). There were no significant differences in DBP, heart rate, and lipid profile. Follow-up time was longer in patients with regression of LVH ($P=0.003$; Table 1). Similar results were obtained when pooling patients with reduction in LVMi <5 $g/m^{2.7}$ with those with persistent LVH (Table S1).

Lack of LVH regression was associated with greater LVMi and carotid IMT ($P<0.01$; Table 1) as well as lower GFR at baseline ($P<0.05$; Table 2). There was no significant difference in relative wall thickness and proportion of concentric LV geometry at baseline (Table 2). In contrast, pooled patients without either reduction or normalization of LVMi exhibited higher carotid IMT, lower LVMi at baseline, and less-common concentric LV geometry (Table S2). At follow-up, concentric geometry was significantly more common among patients with lack of LVH regression (Table 2) or those without either reduction or normalization of LVMi (Table S2). Average baseline arterial stiffness did not differ between patients without or with LVH regression (Table 2), whereas it was higher when also considering patients without significant reduction of LVMi (Table S2).

Less reduction in both SBP and DBP during follow-up and less optimal BP control were observed in patients with lack of regression of LVH (Table 3), and in those without either reduction or normalization of LVMi (Table S3), though the number and types of antihypertensive medication did not differ significantly between these groups, except for beta-blocker being more common in patients without reduction or normalization of LVMi.

Covariates of Lack of LVH Regression

In logistic regression analysis, older age, female sex, obesity, lack of BP control, less reduction of systolic BP during follow-up, and higher baseline LVMi and carotid IMT were

Table 1. Clinical Characteristics of the Study Participants With or Without Regression of LVH During Follow-up

Variables	No LVH Regression (N=1878)	LVH Regression (n=295)	*P* Value
Age, y	58±10	54±10	<0.0001
Women, %	50	36	<0.0001
Duration of hypertension, y	8.1±7.6	6.3±7.6	<0.0001
BMI, kg/m^2	29.6±4.4	27.9±3.5	<0.0001
Obesity (BMI ≥30 kg/m^2), %	42	24	<0.0001
Isolated systolic hypertension baseline, %	20	14	0.021
Diabetes mellitus, %	15	9	0.019
MetS, %	39	26	<0.0001
Smoking, %	15	21	0.032
Systolic BP baseline, mm Hg	149±20	146±21	0.015
Diastolic BP baseline, mm Hg	90±12	91±12	0.411
Mean follow-up systolic BP, mm Hg	140±13	135±11	<0.0001
Mean follow-up diastolic BP, mm Hg	84±7	83±6	0.031
Heart rate baseline, bpm	73±11	74±12	0.296
Total-cholesterol, mg/dL	206±39	202±37	0.126
LDL-cholesterol, mg/dL	128±36	125±33	0.113
Triglycerids, mg/dL	141±76	137±75	0.369
Follow-up time, y	5.4 (3.2–9.3)	6.5 (4.1–9.9)	<0.001
No. of visits per patient	7.0 (5.0–12.0)	8.0 (5.0–12.0)	0.098
No. of visits per patient year	1.3 (1.1–1.8)	1.3 (1.1–1.5)	<0.001
No. of echocardiograms	3 (2–5)	4 (3–5)	<0.001

BMI indicates body mass index; BP, blood pressure; LDL, low-density lipoprotein; LVH, left ventricular hypertrophy; MetS, metabolic syndrome.

independently associated with lack of LVH regression. These associations were independent of diabetes mellitus, duration of hypertension, presence of ISH, follow-up duration (all variables that were significant in univariate analysis), and also independent of number and class of antihypertensive medication (Table 4). In the same model of analysis, the independent significant covariates of lack of either reduction or normalization of LVMi were older age, female sex, obesity, ISH, lack of BP control, less reduction in SBP during follow-up,

Table 2. Cardiac and Vascular Structural Characteristics of the Study Participants With or Without Regression of LVH During Follow-up

Variables	No LVH Regression (N=1878)	LVH Regression (n=295)	*P* Value
Carotid IMT max 1, mm	1.8±0.8	1.6±0.7	<0.0001
LV mass index baseline, g/m$^{2.7}$	56.8±7.7	52.7±4.9	<0.0001
Concentric baseline LV geometry, %	16	19	0.171
Concentric follow-up LV geometry, %	14	6	<0.001
e-GFR, mL/min per 1.73 m^2	73±17	75±17	0.048
Pulse pressure/stroke index, mm Hg/mL×m$^{-2.04}$	2.12±0.63	2.09±0.57	0.401

e-GFR indicates estimated glomerular filtration rate; IMT, intima media thickness; LV, left ventricular; LVH, left ventricular hypertrophy; max, maximum.

lower baseline LVMi, higher carotid IMT, and less-frequent prescription of beta-blocker (Table S4).

Discussion

This study demonstrates that clear-cut LVH regression was infrequently achieved in the CSN registry, a tertiary care

Table 3. Blood Pressure and Distribution of Antihypertensive Medication Among Patients With or Without Regression of LVH During Follow-up

Medication	No LVH Regression (N=1878)	LVH Regression (n=295)	*P* Value
Reduction in SBP during follow-up, mm Hg	9±17	11±17	0.019
Reduction in DBP during follow-up, mm Hg	6±10	8±10	0.015
Optimal BP control baseline, %	51	47	0.436
Optimal BP control during follow-up, %	87	92	0.007
No. of antihypertensive drugs	1.9±1.0	1.8±1.0	0.057
Beta-blocker, %	28	24	0.143
Ca-channel blockers, %	32	28	0.155
ACE inhibitors, %	42	36	0.062
ARB, %	35	40	0.129
Diuretics, %	54	52	0.508

ACE indicates angiotensin converting enzyme; ARB, angiotensin AT1 receptor blocker; BP, blood pressure; Ca, calcium; DBP, diastolic blood pressure; LVH, left ventricular hypertrophy; SBP, systolic blood pressure.

Table 4. Uni- and Multivariable Regression Analysis of Covariates Associated With Lack of LVH Regression in Treated Hypertensive Subjects

	Univariable			Multivariable					
				Model 1			Model 2		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Age, y	1.04	1.03 to 1.05	<0.001*	1.03	1.02 to 1.05	<0.001	1.03	1.02 to 1.05	<0.001
Female sex	1.73	1.35 to 2.24	<0.001*	2.55	1.88 to 3.45	<0.001	2.65	1.94 to 3.62	<0.001
BP control (n/y)	0.55	0.35 to 0.85	0.008*	0.52	0.32 to 0.87	0.012	0.52	0.31 to 0.86	0.011
LVMi, g/m$^{2.7}$	1.13	1.10 to 1.16	<0.001*	1.16	1.12 to 1.20	<0.001	1.16	1.12 to 1.20	<0.001
Obesity (n/y)	2.25	1.69 to 2.98	<0.001*	1.98	1.45 to 2.70	<0.001	2.06	1.51 to 2.82	<0.001
Carotid IMT, mm	1.55	1.29 to 1.86	<0.001*	1.28	1.03 to 1.59	0.028	1.28	1.02 to 1.59	0.032
Diabetes mellitus (n/y)	1.61	1.08 to 2.42	0.020*						
Isolated systolic hypertension (n/y)	1.51	1.06 to 2.13	0.022*						
Duration of hypertension, y	1.04	1.02 to 1.06	<0.001*						
No. of antihypertensive drugs	1.12	0.99 to 1.00	0.075				0.88	0.62 to 1.25	0.477
Follow-up time, y	0.96	0.93 to 0.99	0.004						
Reduction in SBP (5 mm Hg)	0.95	0.90 to 0.99	0.015*	0.93	0.89 to 0.99	0.014	0.93	0.89 to 0.99	0.015
Reduction in DBP (5 mm Hg)	0.90	0.83 to 0.98	0.013*						
Beta-blocker	1.24	0.93 to 1.65	0.144				0.70	0.45 to 1.09	0.114
Ca-channel blockers	1.22	0.93 to 1.60	0.155				0.75	0.48 to 1.17	0.204
ACE inhibitors	1.27	0.99 to 1.64	0.062				0.85	0.61 to 1.17	0.312
ARB	0.82	0.64 to 1.06	0.130				1.14	0.70 to 1.62	0.477
Diuretics	1.09	0.85 to 1.34	0.508				1.21	0.73 to 2.02	0.456

*Model 1: including variables that were significant in univariable logistic analysis.
Model 2: also including number and class of medication forced into the Model 1. ACE indicates angiotensin converting enzyme; ARB, angiotensin AT1 receptor blocker; BP, blood pressure; Ca, calcium; DBP, diastolic blood pressure; LVH, left ventricular hypertrophy; LVMi, LV mass index; OR, odds ratio; SBP, systolic blood pressure.

center for arterial hypertension, despite an overall good BP control. LVH regression was found only in 14% of hypertensive outpatients with LVH at baseline, followed for a median of 67 months, and this proportion raised to only 23% when considering also patients remaining with LVH but reducing their initial LVMi of at least 5 g/m$^{2.7}$.

The phenotype of the hypertensive patient who did not experience LVH regression was typically an old, obese woman, with suboptimal systolic BP control over time, established vascular damage, and higher values of LVMi, reflecting high cardiovascular risk. No independent associations were found with diabetes mellitus, ISH, reported duration of hypertension, and number and types of antihypertensive medications. In patients with severe LVH, a significant reduction of LVMi can occur without necessarily achieving normal values. This was the reason to perform a secondary analysis displayed in the appendix, accounting also for a significant reduction (≥5 g/m$^{2.7}$) in LVMi. Both analyses indicate that reduction of LVMi or normalization of LVH is more difficult to achieve in old females with high cardiovascular risk and poor BP control, but also that the lack of regression of LVH or lack of significant reduction in LVMi exposes patients to higher cardiovascular risk.

The low proportion of LVH regression in hypertensive patients from the CSN registry is in line with results from a randomized, clinical trial, the Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) study,[9] demonstrating lack of LVH regression in subgroups of hypertensive patients with MetS. In addition, lack of LVH regression despite BP control was also demonstrated in an unselected population-based cohort with high prevalence of obesity and diabetes mellitus.[11] The negative independent impact of female sex on LVH regression, shown in Table 4, is also consistent with previous results demonstrating less LVH regression in elderly women, and in patients with diabetes mellitus, obesity, and other metabolic disturbances, all independent of BP control.[9,10,30]

In exploratory analysis, ISH was more common in hypertensive patients with lack of LVH regression, supporting a previous finding from the LIFE study.[31] However, after controlling for critical covariates (obesity and BP control during treatment), the negative effect of uncontrolled BP on

the possibility of LVH regression emerged as the key reason of lack of regression, being very common in patients with ISH.[32,33]

The disappointing low rate of LVH regression in the CSN registry is in apparent contrast with previous findings from a number of randomized, clinical trials in arterial hypertension, in which treatment induced a substantial reduction of LVM.[7,34,35] For instance, previous clinical trials have demonstrated echocardiographic LVH regression in 50% to 60% of hypertensive patients with LVH during antihypertensive treatment.[4,36] The relatively low reduction in BP achieved during antihypertensive treatment may also partly explain the observed low rate of LVH regression. Analysis performed in the Strong Heart Study, a population-based cohort, showed similar findings also in the context of target BP control.[11] Among the Strong Heart Study participants with baseline LVH, 85% remained with LVH (defined in that study as reduction of 5% of the initial value) at the follow-up, compared to the 15% who exhibited reduction of the initial LVMi ($P<0.0001$). A meta-analysis of 4 clinical trials assessing echocardiographic regression of LVH reported only 8% LVH regression.[37]

The fact that LVH regression demonstrated in placebo-controlled, randomized, clinical trials and several meta-analyses could not be confirmed in our analysis of hypertensive patients from a large, real-word registry collected in a tertiary care center could be expected. The selection imposed in clinical trials and meta-analyses remains an important problem when transferred to the real world in patients with characteristics and risk profile that do not reflect the trial selection.[12] The CSN registry recruits from a number of hypertensive outpatient clinics treating patients with a variety of clinical presentations, including a number of associated conditions that would not fulfill the selection criteria required by the major trials. The patient selection is of critical importance to try weighting for major confounders, but the majority of hypertensive patients seen in routine clinical practice would not be eligible for randomized, controlled trials.[38] Thus, the results of clinical trials, which have strong internal validity, are suggested to be tested for external validity in observational studies.[12]

Another important characteristic of outpatients in a tertiary care center is their clinical history. Unlike patients included in many clinical trials who often had short duration of hypertension and were untreated, the CSN patients have, on average, 8 years duration of hypertension and, especially important, they come to the outpatient clinic of the Hypertension Center of the Federico II University Hospital after variable periods and cycles of antihypertensive treatment. Thus, in this context, hypertensive LVH reflects consolidated organ damage possibly resistant to previous therapy, though often the prescribed therapy before admission to our hypertension center was not effective for optimal BP reduction. However, of course, we cannot determine how many patients could have had their LVMi significantly reduced before their first contact with our hypertension center.

Overall, results from registries are important to derive more realistic expectations on treatment effect, and to identify the characteristics of high risk individuals in a setting closer to clinical practice in the real world.[12]

Our findings also indirectly confirm that BP and target organ damage control are better achieved when arterial hypertension is managed at an early stage and in the absence of other metabolic abnormalities,[32,39] whereas antihypertensive therapy is less effective when the disease has progressed toward more-advanced stages.[40]

Whether and how much metabolic, nonhemodynamic stimuli participate in the development of irreversible myocardial structural changes cannot be explored in this type of study, but some inference can be attempted. Increase in LVM and consequent development of LVH is a process not exclusively related to sarcomere-dependent cardiomyocyte hypertrophy, especially in obese individuals, in whom other cellular and structural components, including extracellular matrix, fibroblasts, adipocytes, as well as increase in cardiomyocyte size attributed to fat infiltration, are involved.[41–43] Thus, BP control alone may not be sufficient to induce regression of LVH when other metabolic factors also influence LV geometry.[44] Among them, visceral fat might have particular importance. In a subpopulation of individuals with severe alteration of body composition and substantial excess of body fat associated with relative fat-free mass deficiency, often referred to as "sarcopenic obesity," paradoxically LVM is increased and LV geometry is concentric, independent of BP values, suggesting that in these subjects modification of LV geometry are not induced by hemodynamic factors.[45] It is also interesting that sarcopenic obesity is a specific characteristic of obese women.[45]

Study Limitations

As noticed above, this is an observational study including hypertensive patients enrolled in a large, open, outpatient registry; consequently, the follow-up time for the individual patients differs. To account for the potential bias introduced by the difference in follow-up time, we included follow-up time in the multivariable models, because time-varying echocardiographic analysis of LVMi could not be run. In addition, we only included patients with at least 24 months of follow-up, because we know from previous randomized, clinical trials that LVH regression mainly occurs during the first 24 months of follow-up.[7,9] In addition, observational studies are, in general, well suited to identify predictors in real-word contexts, which was the aim of our study. In particular, one of the advantages of observational studies compared to

controlled studies is the generation of results into a real-world context, which allows generalization and provides external validation for clinical trials.[12]

Classification and reclassification of LVH by echocardiography, based on single assessments, might be challenging, because of the intrinsic noise in the measurement. However, echocardiographic assessment of LVM has previously been demonstrated to maintain sufficient reliability to be used in clinical practice. In the RES study, we found that test-retest changes in LVMi of around 10% in single patients have a reasonable chance to exceed the possible technical error and, in highly skilled contexts, have clinical relevance.[46]

Conclusion

LVH regression occurred in 14% of treated hypertensive patients with initial LVH during follow-up. Patients who experienced lack of LVH regression during antihypertensive treatment were older, more often female with more end-organ damage, and suboptimal BP control and exhibited an increased risk of cardiovascular events. Development and maintenance of hypertensive LVH is multifactorial and partly independent of BP, in particular, in hypertensive patient with obesity and/or clustering of cardiovascular risk factors, indicating that management of arterial hypertension cannot be limited to BP control, as already suggested by guidelines.[6] Eventually, there is the need to implement specific studies on women who seem to be particularly exposed.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Clinical characteristics of the study participants without or with ≥5 g/$^{m2.7}$ regression of LVMi or normalization of LVMi during follow-up

Variables	No LVMi reduction (N = 1684)	LVMi reduction (N = 489)	P-value
Age (years)	58±10	55±11	<0.001
Women (%)	50	39	<0.001
Duration of HT (years)	8.1 ±7.6	7.0± 7.6	0.006
BMI (kg/m^2)	29.5±4.4	28.7±4.1	<0.001
Obesity (BMI ≥ 30 kg/m^2) (%)	41	32	<0.001
Isolated systolic HT baseline (%)	20	13	<0.001
Diabetes (%)	16	11	0.028
Metabolic Syndrome (%)	39	32	0.014
Smoking (%)	14	19	0.055
Systolic BP baseline (mmHg)	149± 19	148 ±21	0.609
Diastolic BP baseline (mmHg)	90±12	92±12	0.004
Mean follow-up systolic BP (mmHg)	141±13	137±12	<0.001
Mean follow-up diastolic BP (mmHg)	84±7	84±7	0.378
Heart rate baseline (bpm)	73±11	74±12	0.691
Total-Cholesterol (mg/dL)	206±39	201±37	0.013
LDL-cholesterol (mg/dL)	129±37	125±33	0.021
Triglycerids (mg/dL)	141±75	137±77	0.286
Follow-up time (years)	5.4 (3.2-9.2)	6.3 (3.6-9.7)	0.002
Number of visits pr patient	7.0 (5.0-12.0)	8.0 (5.0-13.0)	0.011
Number of visits pr patient year	1.3 (1.1-1.8)	1.3 (1.1-1.6)	0.080

Number of echocardiograms	3 (2-5)	4 (3-5)	<0.001

HT: Hypertension; BMI: Body mass index; BP: Blood pressure.

Table S2. Cardiac and vascular structural characteristics of the study participants without or with ≥5 g/m$^{2.7}$ regression of LVMi or normalization of LVMi during follow-up

Variables	No LVMi reduction (N = 1684)	LVMi reduction (n = 489)	P-value
Carotid IMT max 1 (mm)	1.8 ±0.8	1.7 ±0.7	0.024
LV Mass Index baseline (g/m$^{2.7}$)	55.7± 6.4	58.0 ±10.0	<0.001
Concentric baseline LV geometry (%)	15	21	0.001
Concentric follow-up LV geometry (%)	14	7	<0.001
e-GFR (mL/min/1.73 m^2)	73± 17	75± 17	0.073
Pulse Pressure / Stroke index (mmHg/mL×m$^{-2.04}$)	2.14±0.63	2.06±0.59	0.008

IMT: Intima media thickness; LV: Left ventricular; e-GFR: estimated glomerular filtration rate.

Table S3. Blood pressure and distribution of antihypertensive medication among patients with or without ≥5 g/m$^{2.7}$ regression of LVMi or normalization of LVMi during follow-up

	No LVMi reduction (N = 1684)	**LVMi reduction (n = 489)**	**P-Value**
Reduction in SBP during follow-up (mmHg)	8±16	12±17	<0.001
Reduction in DBP during follow-up (mmHg)	6±10	10±10	<0.001
Optimal BP control baseline (%)	48	46	0.608
Optimal BP control during follow-up (%)	87	90	0.032
Number of antihypertensive drugs	1.9± 1.1	1.9 ±1.0	0.653
Beta-blocker (%)	28	24	0.035
Ca-channel blockers (%)	32	30	0.432
ACE* inhibitors (%)	41	41	0.977
ARB ** (%)	35	38	0.226
Diuretics (%)	53	54	0.586

*ACE: Angiotensin converting enzyme

** ARB: Angiotensin AT1 receptor blocker

Table S4. Univariable and multivariable regression analysis of covariates associated with lack of LVMi reduction or normalization of LVH in treated hypertensive subjects.

	Univariable			**Multivariable**					
				Model 1			**Model 2**		
	OR	95%CI	p	OR	95%CI	p	OR	95%CI	P
Age (years)	1.03	1.02-1.04	**<0.001**	1.03	1.01-1.04	<0.001	1.03	1.02-1.04	<0.001
Female sex	1.57	1.28-1.93	**<0.001**	2.22	0.99-1.57	0.060	1.39	0.98-1.57	0.072
BP control (n/y)	0.67	0.50-0.97	**0.033**	0.52	0.35-0.75	0.001	0.53	0.37-0.78	0.010
LVMi (g/m$^{2.7}$)	0.96	0.95-0.98	**<0.001**	0.95	0.94-0.97	<0.001	0.95	0.94-0.97	<0.001
Obesity (n/y)	1.50	1.22-1.86	**<0.001**	1.74	1.37-2.21	<0.001	1.78	1.40-2.26	<0.001
Carotid IMT (mm)	1.32	1.14-1.52	**<0.001**	1.22	1.03-1.44	0.024	1.22	1.02-1.45	0.025
Diabetes (n/y)	1.42	1.04-1.93	**0.028**						
Isolated systolic hypertension (n/y)	1.67	1.25-2.22	**<0.001**	1.81	1.29-2.54	0.001	1.76	1.25-2.48	0.001
Duration of hypertension (years)	1.02	1.01-1.04	**0.006**						
Number of antihypertensive drugs	1.02	0.93-1.13	0.671				1.20	0.90-1.61	0.184

Follow-up time (years)	0.97	0.95-1.00	0.031						
Reduction in SBP (5 mmHg)	0.93	0.89-0.96	**<0.001**	0.96	0.92-0.99	0.034	0.95	0.91-0.99	0.021
Reduction in DBP (5mmHg)	0.86	0.80-0.93	**<0.001**						
Beta-blocker	1.29	1.02-1.63	**0.035**				1.61	1.14-2.33	0.024
Ca-channel blockers	1.09	0.89-1.36	0.432				1.41	0.98-2.04	0.288
ACE inhibitors	1.00	0.81-1.22	0.977				1.14	0.87-1.47	0.351
ARB	1.14	0.93-1.41	0.226				1.21	0.91-1.61	0.184
Diuretics	1.05	0.86-1.30	0.586				1.09	0.72-1.64	0.702

Model 1: including variables that were significant in univariable logistic analysis (in boldface).

Model 2: also including number and class of medication forced into the Model 1.

Left Ventricular Hypertrophy Regression During Antihypertensive Treatment in an Outpatient Clinic (the Campania Salute Network)

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